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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/085,476
Filing Date: February 27, 2002
Appellant(s): DE FRANCESCO ET AL.

Sheldon O. Heber
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/18/2006 appealing from the Office action mailed 10/28/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Tomei et al., Journal of Virology 67(7): 4017-4026, July 1993.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12, 14, 17, 18, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993).

Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa. Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Tomei et al. further teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and translate NS5B, described by SEQ ID NO: 1 (see page 4020, Figure 1 and also Figure 3A).

One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place *in vitro,* in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF. The

expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. One of ordinary skill at the time of invention would have been motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The motivation for the addition of ribonucleotide substrates and a RNA template comes from the suggestion by Tomei et al. that the NS5B encodes a RNA-dependent RNA polymerase. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place *in vitro* in the presence of potential target molecules which may inhibit the action of the NS5B protein as a means of identifying potential

therapeutics to be used against the NS5B protein and HCV. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. A reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above.

(10) Response to Argument

Appellants traverse the current rejection of claims 12, 14, 17, 18, 22 and 23 as obvious under 35 U.S. C. 103 based on Tomei et al. based on a number of different reasons.

Prior to responding to appellants position, it is noted that current claims 12 and 22 are drawn to those methods comprising **incubating** *in vitro* a composition comprising HCV NS5B recombinant protein, ribonucleotide substrates, an RNA template and a test compound, under conditions suitable to produce NS5B RNA-dependent RNA polymerase activity in the absence of said compound and **measuring** the ability of said test compound to affect said NS5B RNA-dependent RNA polymerase activity. The claimed methods do not require that RNA dependent RNA polymerase activity be identified or even produced, but rather they only require measuring the ability of a test compound to affect RNA-dependent RNA polymerase activity, which may be measured by various means. It is again noted that the measurement of such an activity,

does not dictate or require that such an activity exists, but just that it is assayed for. It is further noted that with respect to the referred to "test compound", the claims do not place any limitations on the test compound, such that the test compound may be anything, including buffers, ribonucleotide substrates and even the RNA template used in any RNA-dependent RNA polymerase activity assay.

Appellants submit that claim 22 distinguishes Tomei et al. by employing HCV NS5B Expressed in either a eukaryotic or prokaryotic heterologous system. In response to this initial submission appellants are reminded that the current rejection is based upon obviousness, not anticipation and so it is recognized that claim 22 distinguishes Tomei et al., however, claim 22 continues to be obvious over Tomei et al. for the reasons previously made of record and repeated herein. As previously stated, Tomei et al. teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and translate NS5B, described by SEQ ID NO: 1, in a eukaryotic heterologous system.

Appellants further submit that the prior art expresses doubt as to whether recombinantly expressed NS5B is an authentic HCV protein and the prior art fails to provide data concerning NS5B activity. Appellants submit that these prior art uncertainties concerning the relevance of recombinantly produced NS5B to a naturally occurring HCV protein impacts both motivation to modify Tomei et al. and the likelihood of success in modifying Tomei et al. In response to this line of reasoning, appellants are again reminded that claim 22 does not require that RNA dependent RNA

polymerase activity be identified or even produced, but rather claim 22 only requires measuring the ability of a test compound to affect RNA-dependent RNA polymerase activity, which may be measured by various means. It is again noted that the measurement of such an activity, does not dictate or require that such an activity exists, but merely that it is assayed for. Accordingly the mere measurement of RNA-dependent RNA polymerase activity comprising HCV NS5B, ribonucleotide substrates, an RNA template and a test compound (i.e. any buffer or reaction component) reads on the claims and as previously stated, such is obvious for the reasons of record.

In supporting appellants position, appellants submit that Tomei et al. concerns HCV polyprotein processing using a recombinant expression system and does not provide data concerning recombinantly expressed NS5B activity or indicate that NS5B could be used to look for RNA-dependent RNA polymerase activity inhibitors.

Appellants submit that instead of considering the relevance of the observations provided by Tomei et al., in light of the prior art, the rejection focuses on certain statements provided in the prior art and assumes motivations. Appellants support this position by pointing out the significant uncertainty expressed in the prior art as a whole concerning whether recombinantly expressed NS5B is an authentic HCV protein or a recombinant expression artifact. Appellants submit that this uncertainty goes against both motivation and a reasonable expectation of success in modifying Tomei et al. to obtain the claimed assay.

Appellants further submit the apparent failure and difficulty encountered by others and long-felt need to further illustrate the non-obviousness of the claimed assay.

Appellants repeat that the provided rejection improperly failed to consider prior art uncertainty as to whether recombinantly expressed NS5B is an authentic HCV protein or a recombinant expression artifact and failed to consider secondary considerations.

In response, to each of appellants' points, appellants are reminded that the examiner is aware that the motivation presented in the current rejection may not be the same as that referred to by appellants or even the reference on which the rejection is based. Appellants are again reminded that the claimed methods **do not require that RNA dependent RNA polymerase activity be identified or produced**, but rather they only require measuring the ability of a test compound to affect RNA-dependent RNA polymerase activity, which may be measured by various means, none of which require the successful production or identification of RNA-dependent RNA polymerase activity. Thus the motivation upon which the rejection is based is the referred to motivation to assay the NS5B protein for RNA-dependent RNA polymerase activity, and nothing more.

As previously stated, Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa, one of which, the NS5B region, contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and Tomei et al. suggests that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function

in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5).

One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase, wherein said incubation takes place *in vitro* in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. One of ordinary skill at the time of invention would have been further motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a

manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place *in vitro* in the presence of potential target molecules which may inhibit the action of the NS5B protein as a means of identifying potential therapeutics to be used against the NS5B protein and HCV. Again, the motivation for why one of skill in the art would be interested in the function of the NS5B ORF, is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF, is a prime target for the development of therapeutics against HCV. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above. Further, appellants are reminded that the claims are merely drawn to methods of incubating and measuring, for which the expectation of success is quite high (i.e. a 'positive" result is not required to practice the claimed method).

Each of appellants points, 1) that Tomei et al. concerns HCV polyprotein processing using a recombinant expression system, 2) that significant uncertainty expressed in the prior art as a whole concerning whether recombinantly expressed NS5B is an authentic HCV protein or a recombinant expression , 3) the apparent failure,

difficulty encountered by others and long-felt need to further illustrate the non-obviousness of the claimed assay and 4) the failure to consider prior art uncertainty as to whether recombinantly expressed NS5B is an authentic HCV protein or a recombinant expression artifact as well as secondary considerations are all acknowledged, and appreciated. However, it is further acknowledged that appellants continue to argue these points in light of motivation and reasonable expectation of success as related to a method, step or limitation that does not exist. That is the production or identification of RNA-dependent RNA polymerase activity. As has been repeated throughout prosecution and above, this is not required to practice that claimed method, and thus any argument directed towards such a requirement is found non-persuasive.

Appellants further submit that claim 23, which depends from claim 22, further distinguishes Tomei et al. by measuring primer independent RNA-dependent RNA polymerase activity. Appellants submit that this rejection amounts to an invitation to experiment to characterize NS5B activity and that the prior art fails to even demonstrate that NS5B provides for RNA-dependent RNA polymerase activity, thus the skilled artisan would not be motivated to further characterize the enzyme, or set up an assay to look for inhibitors by measuring primer independent RNA-dependent RNA polymerase activity. Appellant's complete argument with respect to claim 23 is acknowledged, however, continues to be found non-persuasive based upon the same reasons stated above for claim 22. As stated above, the teachings of Tomei et al. and any uncertainties of the prior art are recognized, however, not found relevant to those

methods that are deemed obvious in light of Tomei et al. As repeated above, the identification or production of RNA-dependent RNA polymerase activity is unnecessary to practice the claimed methods. The claimed methods only require assaying for RNA-dependent RNA polymerase activity. Further the obvious methods of assaying NS5B for RNA-dependent RNA polymerase activity as discussed above, would inherently also measure primer independent RNA-dependent RNA polymerase activity. In fact any measure of RNA-dependent RNA polymerase activity will measure such activity that is primer independent. This is in contrast to primer dependent RNA-dependent RNA polymerase activity, which would only be measured in the presence of a primer. Thus as discussed above, the claims which appellants appear to believe are further limiting, and refer to primer independent RNA-dependent RNA polymerase activity, in fact are obvious for the same reasons that the base claim 22 is obvious, because the claimed method does not require the identification or production of any activity, not even an activity more specific than RNA-dependent RNA polymerase, such as primer independent RNA-dependent RNA polymerase activity.

Appellants further submit that claims 12, 17 and 18 further distinguish Tomei et al. by employing NS5B purified to apparent homogeneity. Appellants submit that claim 12 is along the lines of claim 22, but indicates that NS5B is purified to apparent homogeneity and claims 17 and 18 depend from claim 12 and are argued in combination with claim 12. Appellants submit that the reference to purified to homogeneity further distinguishes Tomei et al. by indicating a very high degree of purity. In supporting appellants position appellants refer to U.S. Patent No. 5,981,247 and

Chung et al. to point to prior art difficulties in obtaining purified HCV RNA-dependent RNA polymerase.

Appellants complete argument with respect to the reference "purified to apparent homogeneity" and any difficulties associated with such are acknowledged, however, continues to be found non-persuasive on the basis that the referred to claim 12 recites "incubating in vitro a composition comprising a purified HCV NS5B recombinant protein" and by virtue of this language any limitation of purity associated with the referred to NS5B is removed.

Finally, Appellants submit that claim 14, which depends from claim 12, further distinguishes Tomei et al. by measuring primer independent RNA-dependent RNA polymerase activity.

As above for claim 23, appellants submit that this rejection amounts to an invitation to experiment to characterize NS5B activity and that the prior art fails to even demonstrate that NS5B provides for RNA-dependent RNA polymerase activity, thus the skilled artisan would not be motivated to further characterize the enzyme, or set up an assay to look for inhibitors by measuring primer independent RNA-dependent RNA polymerase activity. Appellant's complete argument with respect to claim 14 is acknowledged, however, continues to be found non-persuasive based upon the same reasons stated above for claims12, 22 and 23. As stated above, the teachings of Tomei et al. and any uncertainties of the prior art are recognized, however, not found relevant to those methods that are deemed obvious in light of Tomei et al. As repeated above, the identification or production of RNA-dependent RNA polymerase activity is

unnecessary to practice the claimed methods. The claimed methods only require assaying for RNA-dependent RNA polymerase activity. Further the obvious methods of assaying NS5B for RNA-dependent RNA polymerase activity as discussed above, would inherently also measure primer independent RNA-dependent RNA polymerase activity. In fact any measure of RNA-dependent RNA polymerase activity will measure such activity that is primer independent. This is in contrast to primer dependent RNA-dependent RNA polymerase activity, which would only be measured in the presence of a primer. Thus as discussed above, the claims which appellants appear to believe are further limiting, and refer to primer independent RNA-dependent RNA polymerase activity, in fact are obvious for the same reasons that the base claim 22 is obvious, because the claimed method does not require the identification or production of any activity, not even an activity more specific than RNA-dependent RNA polymerase, such as primer independent RNA-dependent RNA polymerase activity.

Further those arguments presented by appellants with respect to appellants submission that Tomei et al. fails to demonstrate that NS5B (1) corresponds to an authentically produced HCV protein; appellants' point is unclear as to how "whether NS5B corresponds to an authentically produced HCV protein" relates to the currently rejected claims. If applicants are attempting to argue with respect to the expectation of success, as previously stated, Tomei et al. teach that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa and the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific

RNA synthesis and also function in the replication of the viral genome. It would appear that the "NS5B corresponds to an authentically produced HCV protein". With respect to applicants submission that Tomei et al. fails to demonstrate that NS5B (2) is responsible for producing RNA-dependent RNA polymerase activity, as previously stated, Tomei et al. teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome. Applicants are reminded that the current rejection is based on obviousness, not anticipation. With respect to applicants submission that Tomei et al. fails to demonstrate that NS5B (3) can be successfully purified, Tomei et al. teach that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa, and Tomei et al. successfully purify each of these smaller products. While it is acknowledged that purification can be to various degrees, the purification of the NS5 gene products as well as other teachings of Tomei et al. are sufficient to make the rejected claims obvious.

With respect to appellant's comments regarding the apparent failure and difficulty encountered by others as well as a long-felt need, applicants comments are acknowledged, however, not found persuasive. Appellants are reminded that this is a rejection based on the obviousness of the claimed methods and that applicants should argue such that appellant's arguments are clearly directed to the rejection of record, as it applies to the claimed methods.

Finally, as reiterated multiple times above, it is noted that current claims 12 and 22 are drawn to those methods comprising **incubating** *in vitro* a composition **comprising** HCV NS5B recombinant protein, ribonucleotide substrates, an RNA template and a test compound, under conditions suitable to produce NS5B RNA-dependent RNA polymerase activity in the absence of said compound and **measuring** the ability of said test compound to affect said NS5B RNA-dependent RNA polymerase activity. The claimed methods do not require that any RNA dependent RNA polymerase activity be identified or even produced, but rather they only require measuring the ability of a test compound to affect RNA-dependent RNA polymerase activity, which may be measured by various means. It is again noted that the measurement of such an activity, does not dictate or require that such an activity exists, but just that it is assayed for. It is further noted that with respect to the referred to "test compound", the claims do not place any limitations on the test compound, such that the test compound may be anything, including buffers, ribonucleotide substrates and even the RNA template used in any RNA-dependent RNA polymerase activity assay.

Thus claims 12, 14, 17, 18, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993) for the reasons stated previously and above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Richard Hutson

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